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Re: U.S.S.N. 08/249,689

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte PAUL R. SCHIMMEL

Appeal No. 2003-1335
Application No. 08/249,689[1]

ON REQUEST FOR REHEARING

Before WILLIAM F. SMITH, SCHEINER and MILLS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

REMAND TO THE EXAMINER

This application has previously been on appeal (Appeal No. 1997-2396). Following an oral hearing on February 6, 2001, we issued an opinion (dated April 30, 2001) reversing the examiner's rejection of claims 1 and 3-21 for lack of enablement under the first paragraph of 35 U.S.C. § 112, and entering a new ground of rejection against claims 11-13, 17-19 and 21 under the first paragraph of 35 U.S.C. § 112 for failure to provide an adequate written description of the claimed subject matter. As provided for under the then existing provisions of 37 CFR § 1.196(b)(1), appellant opted to continue prosecution of this matter before the examiner, amending the claims and submitting new evidence for the examiner's consideration. The examiner maintained the new ground of rejection, and that rejection, in turn, became the subject of the present appeal.

[1] Application for patent filed May 26, 1994. According to appellant, this application is a continuation of application serial no. 08/129,787, filed September 29, 1993, now abandoned, which is a continuation of application serial no. 07/586,534, filed September 21, 1990, now abandoned. This application is also related to application

Following an oral hearing on July 17, 2003, we issued an opinion (dated October 30, 2003) affirming the written description rejection with respect to claims 11-13 and 21, but reversing the rejection with respect to claims 17-19. In March of 2005, we received a memo, originally dated October 3, 2004, requesting "reconsideration of the decision . . . reversing the rejections of [claims 17-19] in Application Serial No. 08/249,689" from the Directors of Technology Center 1600 (Request, page 1), together with appellant's response to the request for reconsideration, dated November 24, 2004.

We are reluctant to remand this application to the examiner given the already extensive prosecution discussed above, however, for the reasons discussed below, we believe that issues remain that have not been sufficiently developed on the record.

THE CLAIMS

Claims 17-19 (and claims 11 and 12, from which they depend) read as follows:[2]

11. A complementary compound comprising hydrogen bond donor and acceptor sites arranged to specifically bind and inhibit the function of a targeted RNA molecule, wherein the compound is specifically directed to and binds to a critical region of the RNA molecule, located within the minor groove of the RNA molecule, identified by a combination of the primary, secondary and tertiary structure of the critical region.

12. The complementary compound of claim 11 wherein the RNA is selected from the group consisting of mRNA, tRNA, rRNA, and viral RNA.

17. The complementary compound of claim 12 wherein the compound binds to a critical region within the minor groove of the acceptor stem of a tRNA molecule.

18. The complementary compound of claim 17 wherein the tRNA molecule is $tRNA^{Ala}$.

19. The complementary compound of claim 17 wherein the critical region is the G3:U70 base pair.

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[2] While appellant amended certain claims and canceled others in response to our decision of October 30, 2003, this decision concerns the claims as they appeared at the time of the second appeal. Therefore, we will address our comments to claims 17-19 as they appear herein, and in the Appendix to the Substitute Appeal Brief submitted

BACKGROUND

According to the specification, once short, specific regions of an RNA critical to its activity are identified, "compounds specifically inhibiting the RNA can be designed and synthesized using methodology derived from studies using DNA and DNA-protein interactions, in combination with an understanding of the differences in the chemical and physical composition of RNA as compared to DNA" (Specification, page 18). As with DNA, "[t]he chemical basis for the discrimination between different base pairs lies in the order of hydrogen bond acceptor and donor groups across the base pair that is accessible to a protein" (id.). In DNA, the "array of hydrogen bonds permits all four base pairs to be distinguished from each other on the basis of major groove interactions" (id.). "The primary basis for sequence discrimination in RNA is believed to be the minor groove" (id., page 20). RNA "forms [an alpha] helix with major and minor grooves [spiraling] around the axis . . . [and the] [n]ucleotide bases are arranged near the center of the helix with the ribose phosphate backbone on the outside. The bases are planar, perpendicular to the axis, and stacked on one another. Because the helix is in the alpha form, bases and sequences of bases are most accessible from the minor groove, which is wider and more shallow than the major groove" (id., page 2). This "conformation of RNA helices imposes some limits on the potential interactions with protein side chains" (id., page 20), i.e., "the deep groove . . . is too narrow for protein structural motifs such as the α helix to make direct sequence-specific contact" (id.).

The specification gives no examples of the design, synthesis or testing of the claimed complementary compounds, but teaches that once "a critical sequence of the RNA is identified [in the minor groove], [ ] computer modeling is used in combination with

analysis of the targeted RNA sequence to design molecules binding to the targeted RNA by covalent or hydrogen [bonding]" and "[a]ppropriate molecules specifically inhibiting the function of the targeted RNA [that have the required secondary structure and chemical characteristics] are synthesized using known methodology" (Specification, page 5). The claimed complementary "compounds can be organic, inorganic, proteins or even other nucleic acids," but "[i]n the preferred embodiments, compounds are designed as a peptide or organic compound with hydrogen bond donor and acceptor sites arranged to be complementary to the RNA" (id., page 38). In addition, "[s]pecific binding to the targeted molecule can be achieved by including in the [compound a] complementary nucleic acid that forms base pairs with the targeted RNA . . . , or by [including] chemical groups having the correct spatial location and charge" (id.). For peptides, the specification lists a number of proposed hydrogen bond acceptors and donors (id., pages 38-39).

Further according to the specification, the structures of several transfer RNAs (tRNAs) were extensively characterized prior to appellant's invention ("X-ray diffraction analyses have established that virtually all tRNA molecules exist as hydrogen-bonded cloverleaf secondary structures, with tertiary structure formed by additional folding, as depicted . . . by computer modeling in Figure 2B [of the specification]" and "[h]igh-resolution, three-dimensional X-ray structures are available for four tRNAs, showing precise geometries of helical domains and confirming that the stem-loop is precisely folded into an L-shaped three-dimensional conformation with two helices and major and minor grooves" (specification, page 8)). In addition, critical sites had been identified on tRNAs ("For example, studies have demonstrated that the G3:U70 base pair of $tRNA^{Ala}$ is critical for its function" (id., page 5)). According to the specification, "recognition is

mediated principally through contacts made along the inside surface of the tRNA 'L'" and "both helical domains are potential sites for sequence-specific recognition through minor groove differentiation" (id., page 21).

Finally, the specification states that "[c]omputer modeling technology allows visualization of the three-dimensional atomic structure of a selected molecule and rational design of new compounds that will interact with the molecule" when an X-ray crystallographic analysis and force field data are available for the selected molecule (Specification, page 37). "An example of the molecular modeling system . . . consists of the CHARMm and QUANTA programs . . . CHARMm performs [ ] energy minimization and molecular dynamics functions" and "QUANTA performs the construction, graphic modeling and analysis of molecular structure[and] allows interactive construction, modification, visualization, and analysis of the behavior of molecules with each other" (id.).

DISCUSSION

In Enzo Biochem Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002), the Court of Appeals for the Federal Circuit clarified that "[not] all functional descriptions of genetic material fail to meet the written description requirement," and that "the written description requirement would be met for [a claim] . . . if the functional characteristic . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Id. at 1324-25, 63 USPQ2d at 1613. As an example of such a correlation, the court adopted the PTO's internal guidelines for determining compliance with the written description requirement (Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description Requirement," 66 Fed. Reg. 1099 (January 5, 2001)) (Guidelines), at least to the extent

that "the PTO would find compliance with § 112, ¶ 1, for a claim to an 'isolated antibody capable of binding to antigen X,' notwithstanding the functional definition of the antibody, in light of 'the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature.'" Enzo, 296 F.3d at 1324-25, 63 USPQ2d at 1613 (Fed. Cir. 2002).[3]

While the court explicitly adopted Example 16 of the USPTO's Synopsis of Application of Written Description Guidelines (Application of Guidelines), available at http://www.uspto.gov/web/patents/guides.htm), that is not to say that a claim (and its accompanying disclosure) that does not narrowly track Example 16 (or any of the other examples in the Application of Guidelines, for that matter) lacks adequate written descriptive support. The significance of the court's adoption of Example 16 is what it tells us about the factors that should be considered in determining whether or not a claim is supported by an adequate written description. These factors were summarized by the USPTO at page 1106 of the Guidelines, and include "the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure

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[3] The example referred to here (Example 16 of the USPTO's Synopsis of Application of Written Description Guidelines (Application of Guidelines), available at http://www.uspto.gov/web/patents/guides.htm) stipulates that antigen X has been isolated and characterized and that the specification includes a complete protocol for its isolation. "Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature," the Application of Guidelines indicates that the written description requirement is met because "one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X."

and function, and the method of making the claimed invention." According to the Guidelines, "[d]isclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient" to satisfy the written description requirement. Id.

In responding to the new ground of rejection, appellant addressed several of these factors, relying in part on the specification as filed, and on the declarations of Dr. Julius Rebek, an expert in the field of molecular recognition, and Dr. James R. Williamson, an expert on the field of RNA and drug design in general (both submitted April 11, 2002, under the provisions of 37 CFR § 1.132). We relied on the specification and declarations as well in reaching our decision.

In requesting reconsideration of our decision, the Directors of Technology Center 1600 (TC 1600) argue that our decision "is inconsistent with the holding in Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004), which was decided on February 13, 2004 (subsequent to the date of the decision on appeal in the instant application) [and] [f]urthermore, [the decision is based on] an incorrect analogy between description of antibodies whose antigenic target is described and description of a compound whose binding target is described" (Request, pages 5-6). Nevertheless, this is a rapidly evolving, fact-specific area of the law, and we believe that issues remain that have not been sufficiently developed on the record.

First, the Request states that the Court of Appeals for the Federal Circuit "ruled on a fact situation similar to the instant claims" in Rochester, and held that claims "directed to a method of inhibition of cyclooxygenase COX-2 were not supported by an adequate written description because the specification did not describe the structure of

COX-2 inhibitors . . . used in the method" even though "the COX-2 target and methods of assaying for inhibitors" were disclosed (Request, page 7). We recognize that there are a number of striking similarities between the facts of Rochester and the facts of the present case, but we note differences as well – differences which may or may not be significant in light of the factors outlined in the Guidelines. For example, in Rochester there was no identification of a critical site on either COX-1 or COX-2, nor does it appear that there was any requirement that the inhibitor bind any particular site. Here, however, a critical site on a specific tRNA was identified and localized to the minor groove of the acceptor stem of a tRNA and the three-dimensional structure of the tRNA was known in great detail. Moreover, claims 17-19 require that the complementary compounds bind the minor groove at the critical site.[4]

Second, appellant's position is (and has been) essentially that it was well known that "the forces that drive the complementary interactions between antibody/antigen and compound/RNA are the same" and "define their respective structures" (Brief, page 21);[5] that the identification of a specific critical site in the minor groove of an RNA molecule "is parallel to the 'isolation of antigen X'" (id.); and that "[o]nce one of skill in the art knows that one must target the minor groove of the RNA . . . , then one has no difficulty in obtaining compounds" (id., page 23). According to appellant, the declarations "clearly elaborate[ ] upon the present specification's discussion of the forces presented in and by the targeted RNA" (id., page 24). Moreover, appellant argues that the specification, and

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[4] Claim 17 is directed to a complementary compound that binds a critical region within the minor groove of the acceptor stem of a transfer RNA molecule and inhibits its function; claim 18 specifies that the transfer RNA is $tRNA^{Ala}$; and claim 19 identifies the critical site on the $tRNA^{Ala}$ as the G3:U70 base pair.

[5] The Brief referred to herein is appellant's Substitute Appeal Brief submitted

Dr. Williamson's declaration in particular, establish that "there was precedence for targeting to a groove of a nucleic acid helix, although it was not the minor groove, and many software programs were available that make it completely routine to insert the known nucleotide sequence of the target RNA into the program, and have it display structures that define the shape and composition of the claimed inhibitor" (id., page 23). Appellant argues that the specification discloses "functional characteristics [of the claimed compounds] coupled with a correlation between structure and function" (id., page 14), together with a routine method of obtaining the compounds, and therefore satisfies the written description requirement.

The examiner considered appellant's arguments and declarations, but appeared to focus primarily on the fact that "the specification does not provide a working example of the structure . . . of the claimed genus of compounds" (Advisory Action of June 10, 2002) in concluding that "the claimed molecules have not been described by a structural description or by [a] showing of an art-recognized correlation between function and structure" (id.). While the examiner acknowledged that the written description requirement can be satisfied where there is an art-recognized correlation between the function of a binding compound and the structure of its target (as was the case with an antibody and its corresponding antigen in Enzo), the examiner concluded that the facts of the present case are "not analogous to a description of an antibody where the structure of the corresponding antigen is described because the instant claimed genus of compounds is novel and unobvious" (Answer, page 4). If we understand the examiner's rationale, it is that the claimed compound can be an organic, inorganic, protein or nucleic acid molecule – so its general structural characteristics are not specified – while an antigen-specific antibody is a protein with well known structural

characteristics. We would note, however, that the general structure of an antibody reveals little or nothing about the structure of the hypervariable regions of its antigen-combining sites -- arguably the only "novel and unobvious" structural characteristic of an antibody, and that which distinguishes it from other antibodies.

Indeed, the TC's Request notes that "[an] immunized animal will produce antibody molecules that differ from generally known structures of antibodies only in the binding site of the antibodies" but states that "knowledge of the complete structure of the antibody molecule is not required because the antibody molecule can be readily obtained from the immunized animal" (Request, page 9). According to the Request, "unlike methods of making antibodies, the art of making the claimed compounds is not well known and mature" (Request, page 10).

Nevertheless, in responding to the TC's request for reconsideration, appellant notes that the examiner has not provided any evidence in rebuttal on this point, and again relies on the specification and the expert opinions of Drs. Rebek and Williamson as evidence that "that those skilled in the art at the time this application was filed knew or could readily ascertain the structure of the claimed compounds, based on their complementarity to the minor groove of RNA molecules, using available computer software programs" (page 9 of appellant's Response to the TC's Request). We note that the Request does not discuss either declaration.

CONCLUSION

Inasmuch as written description is an evolving, highly fact-specific area of the law, it would be beneficial to have the examiner's analysis of the specification and the declarations of Drs. Rebek and Williamson, and the examiner's views on appellant's response to the TC's Request, in light of the factors outlined in the Guidelines, before determining whether reconsideration of our decision is warranted. In addition, a discussion of the relevance of Rochester that takes into account the differences, as well as the similarities, between the facts of Rochester and the facts of this case would be appropriate.

REMANDED

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

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